

Cover Page

Protocol Number: 7691 Version Date: 12/12/18
Protocol Title: The Effect of rTMS to the Prefrontal Cortex in Alcohol Use Disorder
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Lay Summary

This section is intended to provide a basic overview of the study including a description of its purpose, methods, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

Please also paste of a copy of the Lay Summary into the PRISM PSF Form.

The goal of this study is to investigate a treatment approach for alcohol use disorder (AUD) using a novel form of brain stimulation called deep repetitive transcranial magnetic stimulation (rTMS). We will be targeting frontal regions of the brain that are important for memory and decision making. These brain regions have been shown to be impaired in patients with AUD. Previous studies have mostly used rTMS to a different frontal brain region that is not as deep. These studies have shown that rTMS can reduce craving for alcohol, but there is a lack of research showing that rTMS impacts alcohol consumption.

Our goal in this study is to examine the effect of rTMS on alcohol drinking behavior in an observed laboratory setting. Subjects with AUD will be recruited and admitted to the inpatient unit for the whole study. They will receive 3 weeks of rTMS while in the research unit. Before and after the 3 weeks of stimulation, subjects will participate in a decision-making experiment where they can choose to have an alcoholic drink or the equivalent amount of money that the drink would cost (alcohol self-administration sessions). We will examine their response to alcohol, as well as their performance on tasks that relate to impulsivity and memory. In order to assess target engagement, subjects will also undergo an MRI scan (with spectroscopy) before and after the stimulation period to look at changes in the medial prefrontal cortex of the brain. Subjects will then meet with a study physician for 6 weeks after the study for assessments of alcohol use and medical management sessions.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field, and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall

understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Significance

This project seeks to evaluate the therapeutic potential of repetitive transcranial magnetic stimulation (rTMS) as a potential treatment approach for Alcohol Use Disorder (AUD). Alcohol seeking behavior will be assessed using laboratory alcohol self-administration sessions. Response to alcohol or other drugs in human laboratory paradigms can provide a sensitive indicator of whether a treatment has sufficient promise to embark upon larger, definitive clinical studies. We will also investigate with MRS the changes in GABA in the medial prefrontal (mPFC) and anterior cingulate cortex (ACC). Subjects will be randomized to either sham or active rTMS (10 Hz) and will be admitted to the inpatient unit for study procedures. The MRS scan and alcohol self-administration sessions will be performed before and after the rTMS.

Repetitive Transcranial Magnetic Stimulation and AUD

Previous work with rTMS in AUD has largely been limited to more superficial cortical structures, such as the dorsolateral prefrontal cortex (DLPFC), since deeper structures could not be reached with conventional coils (1). H-coils use a three-dimensional structure to minimize the non-tangential coil elements, which reduces attenuation and allows stimulation of structures that are further from the skull (2). In this proposal we will use the H7 coil, which produces an electric field in the mPFC and ACC (3).

In AUD, the majority of studies using rTMS have investigated craving. Of the seven published studies, five have targeted the DLPFC using high frequency (HF) rTMS, and craving for alcohol was the outcome measure. Four of these studies showed a decrease in craving (4-7) while three showed no effect (8-10). However, these studies have not extensively investigated alcohol intake. There were no reported seizures in any of these studies.

There are limited imaging studies using MRS in AUD that measure GABA or glutamate concentrations. These studies have been mixed, finding a decrease (11) or no change in GABA levels (12) in AUD versus healthy controls. A more recent study found significantly lower GABA levels in the ACC of binge drinkers compared to light drinkers (13). In that study, low GABA levels in the ACC were also associated with greater consequences from alcohol use.

There are also limited studies of rTMS and its effect on GABA in prefrontal brain regions. One open-label study of rTMS with a figure-8 coil stimulating the DLPFC increased GABA levels in the mPFC by 13.8% ($p = 0.013$) (14) in individuals with depression. Another study in treatment-resistant depression using the figure-8 coil did not find any differences in DLPFC GABA levels in the active rTMS group compared to sham, but did find increased GABA to be positively associated with improvement of depression (15).

Overall these studies show that broad regions of the PFC are impaired in AUD. Thus, we have chosen to use the H7-coil, which provides stimulation to broad, deep regions of the PFC. This approach will allow us to use more widespread stimulation, with the rationale that imaging studies in AUD generally implicate broad regions within the PFC rather than discrete brain regions. Additionally, there is evidence that GABA is reduced in AUD and the rTMS may be able to increase GABA levels in the mPFC other prefrontal areas.

Previous research studies have used human laboratory self-administration studies to investigate the effect of naltrexone on AUD. O'Malley et al. (16) was able to detect a significant effect of naltrexone in AUD using an alcohol self-administration paradigm. The self-administration model allows for sensitive detection of clinical effect that has been translated into larger clinical trials.

Based on this previous research experience, we will use this model to investigate the effect of rTMS on alcohol self-administration in the laboratory. We will enroll 16 participants per group (active vs sham rTMS) with moderate to

severe AUD. Participants will receive 3 weeks of rTMS while hospitalized, with a 6 week follow up outpatient phase after discharge.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

Aim 1: Investigation of the effect of rTMS on the choice to self-administer alcohol in the laboratory. AUD volunteers will participate in alcohol self-administration sessions in which they are presented with the choice of alcohol versus a competing reinforcer (money) using methods previously described (16). The sessions will be performed before and after three weeks of rTMS with the H7 coil. Our hypotheses are that active rTMS (n=16) will reduce the number of choices for alcohol during the self-administration sessions compared to sham (n=16).

Aim 2: Investigation of the effect of rTMS on craving for alcohol in the setting of alcohol self-administration sessions. Craving for alcohol will be assessed before and after three weeks of rTMS. Our hypotheses are that active rTMS will reduce craving for alcohol compared to sham.

Aim 3: Investigation of the effect of rTMS on GABA in the mPFC and ACC. AUD volunteers will be imaged with MRS at the start of the study before rTMS, and after completion of 3 weeks of rTMS. We hypothesize the active rTMS will increase GABA levels in the mPFC and ACC compared to sham.

Aim 4: Investigation of the safety of using rTMS in recently detoxified participants with AUD. We will be monitoring the potential for adverse events in this study. Adverse events will be categorized as specified in the "Adverse Event Reporting" section. The primary safety endpoints will include the following: emergence of depression, suicidal ideation, hypomania/mania, or seizure. We will also report on any device malfunction resulting in subject or operator injury. Any resulting common adverse events will be recorded, such as headache, application site pain, and any discontinuations due to adverse events. As described below, we will conduct pre- and post- audiograms and test cognitive function. Data on the severity and duration of each adverse event will be collected, including information on any interventions performed to address the adverse event and whether the event was resolved.

We will include the following *exploratory aims*:

Exploratory Aim 1: Investigation of the effect of rTMS on cognitive control. We will investigate the potential for rTMS to affect executive functioning and implicit cognition.

Exploratory Aim 2: Investigation of the effect of rTMS on abstinence from alcohol following discharge. Participants will be followed for 6 weeks after discharge using medical management as described previously in the COMBINE study (19). Since they will not be taking medication, the visits will focus on overall functioning, importance of abstinence, attendance at support groups, and a review of drinking. This will allow us to investigate the duration of the effect of rTMS after discharge.

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.

You may choose to divide your sample by population (healthy controls vs. subjects) or by procedure (subjects who will have an MRI) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria needs to be numbered and listed in outline form (see Table template below).

<u>CRITERION</u>	<u>METHOD OF ASCERTAINMENT</u>
<u>Inclusion:</u>	
1. Current moderate to severe alcohol use disorder, per DSMV	1. Structured Clinical Interview for DSM V (SCID) and psychiatric assessment
2. Use of alcohol which parallels or exceeds the amount alcohol that will be administered in this study (1 drinking episode per week raising BAL to 0.03 g/dl – approximately 2 drinks within an hour).	2. SCID and psychiatric assessment
3. Age 22-50	3. Identification (driver's license, passport, other state issued identification)
4. Able to give informed consent, and comply with study procedures	4. Psychiatric assessment
5. Medically healthy, with the absence of current or past medical or neurological illnesses (including glaucoma, increased intracranial pressure, liver disease, cardiac disease, or seizure disorders)	5. Medical Assessment, Physical exam, laboratory studies (CBC, electrolytes, liver function tests, urinalysis), ECG. LFTs 2 x normal will be exclusionary.
<u>Exclusion:</u>	
1. Has a contraindication to MRI, such as magnetically reactive implants, which includes metal in head except in mouth (cochlear implant, implanted brain stimulators, aneurysm clips), cardiac pacemakers, implanted neurostimulators and medication pumps, and intracardiac lines.	1. MRI safety screening form, TMS Adult Safety Screen , medical assessment
2. Substance use disorder with substances other than alcohol or nicotine. The current use of sedative-hypnotics or opiates will be	2. SCID, urine screen, psychiatric assessment

exclusionary	
3. Meets DSM-5 criteria for other psychiatric illness, such as major depression, that would interfere with participation.	3. SCID, psychiatric assessment
4. History of seizures of any type	4. Medical history, TMS Adult Safety Screen
5. A family history of epilepsy	5. Medical history, TMS Adult Safety Screen
6. Taking psychotropic medication that would affect resting motor threshold (such as anticonvulsants) or increase risk of seizure (especially tricyclic antidepressants or neuroleptics)	6. Medical/psychiatric history
7. Current suicide risk or a history of suicide attempt within the past 2 years	7. SCID and psychiatric assessment
8. Have unstable physical disorders, including those that are previously undiagnosed, untreated, inadequately treated, or active to an extent which might make participation hazardous. For example, hypertension (a resting blood pressure > 140/90), heart failure, a recent history of myocardial infarction, previous stroke, brain lesions, any history of seizures under any circumstances or low hemoglobin (<11 g/dl for females, < 13 g/dl for males).	8. Medical Assessment, Physical exam, laboratory studies (CBC, electrolytes, liver function tests, urinalysis), ECG.
9. Currently pregnant	9. Medical history, blood pregnancy test, urine HCG. Female patients of childbearing potential must use a barrier method of contraception such as diaphragm, sponge with spermicide, or condom. A urine HCG on admission and twice weekly during admission on all female subjects.
10. History of severe alcohol withdrawal requiring medical care, such as withdrawal seizures, delirium tremens, withdrawal necessitating medical detoxification	10. Medical/psychiatric history, Clinical Institute Withdrawal Assessment for Alcohol (CIWA)
11. A desire to pursue standard treatment for AUD, such as a rehabilitation program or	11. Medical/psychiatric assessment

FDA approved medications for AUD	
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Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

Week 1 Admission to research unit (Mon) 3-day monitored abstinence (Mon-Wed) MRS scan (Thurs) Alcohol self-administration session (Fri)
Weeks 2-3 rTMS delivered on weekdays (Mon-Fri)
Week 4 rTMS delivered on weekdays (Mon-Fri) MRS scan (Thurs) Alcohol self-administration session (Fri)
Week 5 Discharge from research unit (Mon)

Figure 1: Protocol schedule.

Study Design

Overall design:

Individuals with moderate/severe AUD will be enrolled and admitted to the inpatient research unit for the entire study. Half will be randomized to receive high frequency rTMS (n=16) and half will receive sham rTMS (n=16). The procedures are shown in Figure 1. We aim to have 50% males and 50% females.

Screening: Screening will consist of a medical/psychiatric interview and physical exam to rule out medical problems or DSM-5 criteria other psychiatric disorders. All participants will have a urinalysis, urine drug toxicology, ECG, breathalyzer, and blood tests (complete blood count, chemistry/liver profile). A pregnancy test will be performed on all females.

The following assessments will be made: 1). The Alcohol Time Line Follow Back Interview; 2). The Fagerstrom Test for Nicotine Dependence; 3). The Alcohol Use Disorders Identification Test; 4). The Personal Drinking Habits Questionnaire; 5) The Transcranial Magnetic Stimulation Adult Safety Screen; 6). The Clinical Institute Withdrawal Assessment Scale for Alcohol-revised (CIWA-Ar); 7). The Obsessive Compulsive Drinking Scale; 8). The Beck Depression Inventory-II and Beck Anxiety Inventory scales; 9)The MRI Safety Screening Form; 10) Structured Clinical Interview for DSM V (SCID).

Admission: Participants will be admitted to the research unit of the New York State Psychiatric Institute for the duration of the study (**28-35 days**). The research unit provides a therapeutic environment for subjects. Participants are encouraged to attend group activities on the unit, which provide support and coping skills for patients living with psychiatrically illnesses. While on the unit, they will be provided with daily multivitamin and ibuprofen or acetaminophen PRN. We will prospectively track the onset and duration of menses in women using daily rating and weekly hormone levels as routinely done in previous studies. During screening, participants will be informed of the rules of the inpatient unit and that the use of drugs on the unit will result in dismissal. Participants will also be informed that their belongings will be searched prior to admission.

On admission, participants will be closely monitored for signs and symptoms of alcohol withdrawal, using both the Clinical Institute Withdrawal Assessment Scale for Alcohol-revised (CIWA-Ar) and clinical judgment. A CIWA-Ar score greater than 8 and the following vital signs on two separate measures will require treatment with benzodiazepines:

blood pressure > 160/100, pulse >100 bpm, fever. Participants requiring lorazepam for withdrawal will be treated with 2-4 mg Q 6 hours for 4 doses (day 1) followed by 1-2 mg Q 6 hours for 8 doses (days 2-3), as per standard management of alcohol withdrawal. For mild withdrawal, subjects can be given as-needed non-benzodiazepine medications such as hydroxyzine, diphenhydramine, and trazadone for anxiety or insomnia, and ibuprofen for headache. Vital signs and the CIWA will be obtained Q 6 hours, and PRN dosing of lorazepam will be administered if needed. In our experience, the majority of individuals without a prior history of medical detoxification do not require lorazepam to manage withdrawal symptoms. Those who do require lorazepam will only continue in the study if they tolerate the three-day lorazepam dosing described above without rescue. Subjects requiring more lorazepam during the 3-day detoxification period or after the initial 3 inpatient days will be exited from the study and continued to be managed clinically. An additional three days of medication free inpatient monitoring will be required prior to starting the rTMS protocol. Participants requiring longer dosing of lorazepam will be maintained on the inpatient unit they are fully detoxified and then referred for outpatient treatment.

Alcohol self-administration sessions: The participants will be seated in a room that resembles a comfortable living room, the purpose of which is to mimic at-home drinking. The sessions will be performed as described previously (16,17). A priming drink will be provided, consisting of the participant's preferred liquor (80 proof) mixed with fruit juice (1:3 ratio). The volume of alcohol will be determined by the sex, age, and body weight of the participant (16,17) to obtain an estimated BAL of 0.03 g/dl. The amount of alcohol per drink will be calculated by using the Watson equation, which estimates the BAL as a product of total body water and alcohol dose: $A = \frac{TBW}{Bw} * C$, where A = weight of alcohol in grams, TBW = total body water in liters, Bw = fraction of water in the blood, and C is the blood alcohol concentration in grams per liter. For an average sized middle-aged male, this is about 9 grams of alcohol, which is about two-thirds the amount of a standard drink.

Following the priming drink (40 minutes) a tray will be brought in with four drinks and participants will be given one hour to choose between consuming these or money. Each drink will contain enough alcohol to raise BAL by 0.015 g/dl, and they will choose between this and \$5 per drink. After an hour, a second tray of 4 drinks will be presented and another 4 choices between money (\$5 per drink) and alcohol will be made. Participants will be instructed that they can choose to drink as many of the drinks as they desire over each 60 min block or to receive money. Thus, participants can drink up to eight drinks or earn up to US \$40. Money will be provided as an alternative reinforcer in order to provide incentive for not drinking and to investigate the effect of rTMS on the reinforcing value of alcohol (16). Subjects will be assessed prior to return to the research unit to ensure they are not too intoxicated to return to the unit. They will also require a BAL < 0.04 g/dl and will need to pass a field sobriety test. If needed, they can remain in the self-administration lab until that time.

Measures of response to alcohol: The following measures will be obtained at baseline, following the priming dose of alcohol, and at 1, 2, and 4 hours into the sessions: 1) The Alcohol Urge Questionnaire; 2) The Biphasic Alcohol Effects Scale; 3) The Desires for Alcohol Questionnaire with subscales. Breath alcohol levels will be obtained at time 0, and at 30-minute intervals. Impulsivity will be assessed at baseline and 4 hours with 1) The Immediate Memory Task/Delayed Memory Task to measure response initiation; 2) Go/Stop Task to measure response inhibition; 3) Delay Discounting Task, consisting of choices between smaller immediate rewards and larger delayed rewards.

rTMS sessions: All procedures will be administered in a psychiatric hospital where there is access to an emergency team with training and equipment for advanced cardiac life support. The participants will be randomized into 2 groups in a 1:1 ratio by means of randomly permuted blocks: high frequency rTMS or sham treatment, using the deep TMS system (H7 coil) provided by Brainsway, LTD. Each participant is assigned a coded magnetic card, which controls the device and determines whether it delivers active or sham stimulation. All subjects will have earplugs in place during all times. The resting motor threshold (RMT) is determined in each session by applying TMS pulses over the motor cortex (leg motor

area) to induce activation of the tibialis. Subjects will have their motor threshold determined twice weekly. Once the position of the resting motor threshold is determined, the positioning for the prefrontal cortex is achieved by moving the coil 5cm anteriorly while remaining on the midline. For the high frequency rTMS, the following parameters will be used: amplitude =110% of motor threshold, frequency = 10 Hz, train duration = 3 sec with 40 trains /session, 20 sec between trains, total number of pulses = 1200 per session. As described above, participants will receive 15 sessions over 3 weeks. The sham magnetic coil resides in the same helmet along with the active magnetic coil. The sham coil produces a similar clicking noise and delivers superficial stimulation intended to mimic sensations produced by active rTMS. A physician who can manage adverse events, including seizures, will be in house (same building) at all sessions.

At each session and prior to treatment stimulation onset, an alcohol related cue/provocation will be presented to the subject. The alcohol cue/provocation will consist of holding and handling a container of alcohol of the type that the subject is accustomed to drinking for 90 seconds. Immediately after the offset of the alcohol cue/provocation presentation (while memory is reactivated) active or sham rTMS stimulation will be administered.

The staff members who will administer the rTMS will be required to meet all of the following:

- Practical demonstration of ability to perform several determinations of the resting motor threshold, under supervision of a trained investigator or TMS consultant experienced in rTMS.
- Performing at least the first two rTMS study sessions under the supervision of a trained investigator or rTMS consultant experienced in rTMS.
- Working knowledge of the principles and practices of rTMS and the rTMS device being used in the study, including common side-effects and how to recognize them. Knowledge will be based on completed tutorial sessions with the investigators or rTMS consultant experienced in rTMS.
- Knowledge of how to contact the covering physician available in the building.
- Bachelor's degree or higher.

In addition, a physician with the following qualifications will be readily available in the vicinity if the need arises (same building and immediately available). They will have:

- Certification in basic adult life support (e.g. Cardiopulmonary Resuscitation (CPR)).
- Knowledge of seizure first aid, the location of the emergency equipment and medication, how to engage the emergency response system.
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MRS Scanning: Participants will undergo an MRS scan after detoxification during week 1, and again at the end of the rTMS sessions but before the second self-administration session.

Neuroimaging data will be acquired on a **Siemens Magnetom Prisma 3.0T MR scanner, in similar procedures as was** previously performed by our group (18,19). A high-speed localizer imaging series will be obtained, followed by a volumetric T1-weighted spoiled gradient recalled echo scan. Brain spectra containing GABA and Glutamate/Glutamine (Glx) resonances will be acquired. The GABA signals will be quantified relative to the unsuppressed voxel tissue water for absolute quantification. Total scan time should not exceed 60 minutes.

Although our MRI scans are for research purposes, all MR scans are read and interpreted by a radiologist. If the reading yields a finding of immediate clinical concern, the radiologist will provide an report to the PI and Director of the MRI unit. Should an MRI technician or other member of the research team suspect that an MRI scan suggests evidence of a significant lesion, the PI of the study will be notified immediately. A final written transcript of the clinical reading should

be provided within two weeks of the scan. All results will be shared with research participants. Participants requesting a letter will receive one using the language provided by the IRB.

Analysis of the MRS data: The image processing of the MRS data will be performed as described previously (18,19). The data will be combined into single regular time-domain free-induction decay signals, using the INSPECTOR spectroscopy package developed by Dr. Christoph Juchem. Subtraction of the interleaved semi-LASER acquisitions with inhibited and allowed J-modulation will yield the edited GABA C4 H resonance at 3.0 ppm. The areas of the spectral peaks, which are proportional to their respective concentrations, will be obtained by frequency-domain fitting of each resonance to a Gauss–Lorentz line-shape function using the Levenberg–Marquardt nonlinear least-squares algorithm (20). GABA levels in the edited spectra will be expressed as ratios of the peak area relative to that of the simultaneously acquired unsuppressed water signal from the voxel. We will use chi square statistic from the covariance matrix of the curve fitting parameters normalized to the degrees of freedom as described previously (21). To enable groupwise comparisons, the GABA and Glx peak areas will be expressed as ratios relative to the area of the unsuppressed voxel tissue water (W).

Neurocognitive Assessments: The following measures will be administered twice, before rTMS begins and again following completion of rTMS; Working memory (Letter-Number Sequencing); The Delay Discount Assessment; **the Frontal Assessment Battery**; and the Stroop interference task. **The neuropsychological testing will take approximately 2 hours.**

Outpatient Treatment Phase: Subjects will not be discharged until at least 48 hours have passed since the last alcohol self-administration. Participants will be evaluated by a psychiatrist prior to discharge from the unit. Then all participants will begin a 6-week outpatient treatment program. At each weekly visit, alcohol use will be measured with the Time Line Follow-back and breath alcohol, and craving measured with the Alcohol Urge Questionnaire and the Desires for Alcohol Questionnaire. Participants will meet weekly for Medical Management delivered by a study physician, as used previously in the COMBINE study (17). Education will be provided regarding alcohol use disorder and abstinence and attendance at support groups (e.g. 12-step groups) will be encouraged. This is intended to model standard outpatient counseling and to explore relapse to drinking after the inpatient stay as a function of rTMS treatment assignment.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation. In addition, explain procedures for managing subjects who are dropped from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

Participants will be removed from the study and assessed by a member of the clinical staff if, at any stage during participation, they: 1) have significant physical withdrawal symptoms from alcohol; 2) experience significant psychological deterioration as indicated by self-reported anxiety or depressed mood producing clinically significant distress beyond the discomfort typically experienced during alcohol withdrawal; or 3) show functional deterioration as indicated by inability to comply with study procedures. **Participants may also leave the study at any time if they wish to be started in a standard treatment for alcohol use disorder, such as a rehabilitation program or a medication.** After a patient is removed from the protocol, clinical staff will undertake a risk assessment and determine the appropriate course of action, including to admittance to the emergency department of New York Presbyterian or referral for outpatient treatment. Participants may also be discontinued if they fail to follow the study procedures.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at <http://irb.nyspi.org/irbdnn/Policies/GeneticResearch/tabid/96/Default.aspx> for specific guidance and additional information about future use of DNA samples.

During screening we will draw 20 ml for routine medical tests and a plasma pregnancy test (performed twice, at screening and on admission, 15 ml blood) for female participants. Female patients will also have weekly hormone levels (5cc each for 15cc in the study). Thus males will have 20 ml in blood draws and females 50 cc.

Assessment Instruments

List all assessment instruments, indicate who will administer them, and provide an estimate the duration of each. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than is necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

The following standardized assessment instruments will be administered during the screening sessions by trained study staff:

- 1) The Alcohol Time Line Follow Back Interview (20 minutes)
- 2) The Fagerstrom Test for Nicotine Dependence (2 minutes)
- 3) The Alcohol Use Disorders Identification Test (2 minutes)
- 4) The Personal Drinking Habits Questionnaire (5 minute)
- 5) The Transcranial Magnetic Stimulation Adult Safety Screen (2 minutes)
- 6) The Clinical Institute Withdrawal Assessment Scale for Alcohol-revised (CIWA-Ar) (4 minutes)
- 7) The Obsessive Compulsive Drinking Scale (2 minutes)

8) The Beck Depression Inventory-II and Beck Anxiety Inventory scales (5 minutes)

9) MRI Safety Screening Form (2 minutes)

10) Structured Clinical Interview for DSM V (SCID) (30 minutes)

The following measures will be administered during the alcohol self-administration sessions:

1) The Alcohol Urge Questionnaire (2 minutes)

2) The Biphasic Alcohol Effects Scale (2 minutes)

3) The Desires for Alcohol Questionnaire with subscales (2 minutes)

4) The Immediate Memory Task/Delayed Memory Task to measure response initiation (20 minutes)

5) Go/Stop Task to measure response inhibition (10 minutes)

6) Delayed Discounting Task (10 minutes)

The following measures will be administered twice, before rTMS begins and again following completion of rTMS:

1) Working memory (Letter-Number Sequencing) (5 minutes)

2) The Delay Discount Assessment (10 minutes)

3) Stroop interference task (5 minutes)

4) TMS sham questionnaire (2 minutes, only at the end)

5) Frontal Assessment Battery **(10 minutes)**

6) A 5-minute 2-lead ECG performed in order collect data to examine heart rate variability.

8) Audiometry (last evaluation to occur after last rTMS session).

The following measures will be administered weekly during meetings with the MD for medical management sessions:

1) Clinical Global Impression scale

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well-being and safety.

Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

We offer all volunteers the option of obtaining help to abstain drinking multiple times throughout their study participation. Those requesting treatment prior to the start of the study (or at any time during the study) will be referred to treatment and will not be accepted into the study. We will repeat our offer for treatment referral at discharge from the study. We will provide some individual counseling as needed, and, in addition, will refer to treatment clinics those people who indicate a need for help. We will offer referral to a drug treatment program at each of the follow-up visits.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

Subjects are asked about their interest in treatment when they meet with the study physician. Subjects indicating that they are interested in treatment are referred to other studies (that provide treatment) or to treatment clinics.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks first followed by others.

Human subjects involvement, characteristics, and design

During the period of the award, we plan to study 32 subjects with AUD with rTMS and alcohol self-administration sessions in the laboratory. Each subject will also undergo 2 MRI scans. All studies will be performed with the approval of the New York State Psychiatric Institute Institutional Review Board (IRB). We will include 50% female subjects.

Based on our previous studies, we expect that about 38% of our subjects will be non-Hispanic African American, about 27% will be Hispanic, about 35% will be non-Hispanic Caucasian, and <1% will be Asian/Pacific Islanders/Native Americans/Eskimos or Aleuts. Potential research participants will undergo a series of structured interviews during the screening process, in order to determine their eligibility, to ensure that appropriate consent is obtained, and to provide information on the associated risks.

Subjects must be between 18 and 50 years old, given that alcohol is administered in this study. Both males and females will be included in this study. No potential subject will be excluded based on nationality or ethnicity. No special populations will be included.

Source of research material

Blood samples and behavioral measurements will be obtained from the subjects specifically for research purposes, and participants will be so informed. Self-report information, observer records, and physiological and behavioral data collected during treatment sessions will also be used for research purposes. Data will be coded with numbers assigned to each participant, including laboratory studies sent for screening. Only members of the research team, and potentially, reviewers from the IRB will have access to identifiable private information.

Potential Risks

Risks associated with participation in these studies include: 1) the potential effects of high frequency rTMS; 2) risks of alcohol exposure; 3) risk of alcohol withdrawal.

1) Potential effects of high frequency rTMS;

The potential risks of rTMS are as follows:

a. Seizure: This is the greatest concern with rTMS treatment. The incidence of rTMS-induced seizures worldwide is low and roughly comparable to the estimated incidence of spontaneous seizures with antidepressant therapy (0.1– 0.6 %). In addition, rTMS-induced seizures are likely to occur during or just after the rTMS treatment session (rather than after a delay) while our subjects will be hospitalized.

b. Lowering the Seizure Threshold: The use of concurrent medication has been implicated as a risk factor in some of the seizures reported with rTMS. These medications include tricyclic antidepressants and neuroleptics, which are not used in this study. There is also a hypothetical risk of alcohol withdrawal and seizures. The published studies of rTMS in alcohol dependent populations involved different durations of abstinence and no study reported seizures, complications, or adverse events. Additionally, these studies used stimulus parameters (percent above motor threshold) that are the same or higher than that proposed in this study. Thus, the rTMS in this study will be administered by an experienced physician and seizure precautions will be employed (see below). Furthermore, the subjects will be hospitalized and will be carefully monitored. During rTMS administration, staff will also provide visual monitoring for signs of seizures and **twitching of unexpected muscles or continued muscle twitching after stimulation has stopped**. The New York State Psychiatric Institute has emergency response procedures for situations which would include a seizure. The emergency team has a “crash cart” that they bring to emergencies and is notified via building wide loud speaker and mobile phone. 911 would also be called and the subject would be transferred to the Emergency Department at New York Presbyterian, the hospital for the Columbia University Medical Center, which is within the same medical campus. Any seizure that may occur should not deny the participant of employability, motor vehicle licensure, of insurability. If desired, participants may receive a letter to state this.

In the event of a seizure, the following procedures will be employed. A minimum of two staff members will be present, one of whom is an MD. The non- MD staff member will call for medical assistance (911) while the MD will make sure that the participant is on the floor (cannot fall) and will clear the area of all objects. Most seizures will end spontaneously at 1 to 2 minutes. In the event that the 911 responders are not available within 2 minutes and the seizure has not subsided, Lorazepam (which will be stored **in the rTMS suite as well as the SURC/BSU crash cart**) injection 4 mg will be administered IM. **Lorazepam will available in a locked refrigerator in the suite, and will be available and unlocked during each rTMS session. Pharmacy also makes checks on our medication storage procedures.** If seizures continue or recur after a ten to twelve-minute observation period, an additional intravenous dose of 4 mg may be administered until the acute care medical team arrives. Once the subject is stabilized, our team will assist the volunteer with referrals for follow up care.

Brainsway has performed studies using the TMS H-coil device in control subjects and subjects with clinical conditions, including major depressive disorder, schizophrenia, bipolar disorder, addiction, blepharospasm, Parkinson’s disease, and post-traumatic stress disorder (PTSD) (Brainsway, Ltd., unpublished data). The low frequency stimulation was administered to 63 of the 269 subjects (0.2-1 Hz), high intensity TMS (including 3 who also received high frequency treatment), for a total of 112 sessions (average session duration 15 min) and 66,000 pulses. No subjects experienced a seizure. The high frequency (10-20 Hz) and high intensity (<120% of motor threshold [MT]) rTMS was administered to 209 of 269 subjects, who were treated with for a total of 3314 sessions and 143,514 pulse trains. 98 of the 209 subjects received rTMS treatments (1296 sessions, 54,432 pulse trains) without concomitant psychotropic medications (which may lower the seizure threshold) and none experienced a seizure. The remaining 111 subjects received rTMS (2018 sessions, 89,082 pulse trains) in addition to concomitant medications that could affect seizure threshold. Three of these subjects had a seizure. Of these three, one was taking antidepressant medications (venlafaxine, mianserine, mirtazapine), another was taking medications for schizophrenia (olanzapine, citalopram and lorazepam) and the third was taking lithium and clonazepam for bipolar disorder. Nonetheless, given that the H coil has a deeper penetration, it

could be expected to have a higher seizure risk. Thus, to protect against this risk, we have put seizure precautions (described above) in place.

c. Headache: A mild headache, which responding readily to non-opioid analgesics is the most common side-effect reported in depression treatment trials. All volunteers will be treated with NSAIDs as needed for headache.

d. Hearing Impairment: Rapid excitation of the stimulation coil produces clicks that have resulted in transient increase in the auditory threshold, which does not occur if earplugs are used. A previous study assessed the auditory threshold before and after 30 sessions of rTMS (over 6 weeks) in subjects wearing earplugs during stimulation and no significant mean changes were detected. All participants will wear earplugs during the delivery of stimulation. There is a risk for hearing damage to occur if the earplug falls out or is loosened during a session, and participants will be informed to immediately notify staff if this occurs. Staff will regularly check on the comfort level of the subject. If the earplug falls out, or if any hearing discomfort occurs, participants should immediately notify staff and the TMS procedure can be stopped.

e. There is also a risk of visual changes, dental pain, facial numbness, and facial nerve stimulation that may occur with TMS treatment. We will ensure that the helmet sits above the brow line to minimize stimulation around the eyes and face. If any of these symptoms occur, participants should alert the study staff and stop the treatment for an assessment. Participants should also remove all forms of eye makeup especially eyeliner, eye shadow and mascara that may contain ferromagnetic pigments to reduce a risk of pain from reacting with the magnet.

f. Additional risks include scalp pain, dental pain, and rTMS-induced manic effect. Subjects will be evaluated for each of these and treated with over the counter pain medications if required for the scalp and dental pain. Subjects will also be evaluated for an rTMS-induced manic effect. If mania occurs, they will be removed from the protocol and monitored in the hospital until these symptoms resolve. Convulsive syncope has also been reported, and we will take the following measures to prevent this: participants will be asked to immediately report symptoms of syncope (e.g. feeling dizzy, light headed, visual changes) and will be placed in the supine position with elevated legs if syncopal symptoms appear.

2) Risks of alcohol self-administration. Our experience with volunteers tested previously is that the doses of alcohol used do not cause adverse effects. The AUD subjects are required, at the time of admission, to use alcohol in an amount that is much higher than that administered during the study. Further, the participants will be housed on an inpatient unit, and are continuously monitored during the periods during which the alcohol self-administration sessions occur. The amount of alcohol may produce intoxication in subjects. However, they will be on a locked research unit with 24-hour supervision by trained nursing staff and physician on call. The main risk is that of relapse. We will protect against this by administering alcohol in a research laboratory with a physician present and participants are not discharged for 2 days following the last dose of alcohol. Subjects who remain at risk for relapse will not be discharged and will be re-assessed daily. Participants will be given information for outpatient treatment and referrals will be made if desired. Participants will also meet with a study physician for medical management sessions, as outlined above. Education will be provided regarding AUD and abstinence and attendance at support groups (e.g. 12-step groups) will be encouraged. Sessions will include a review of drinking and overall functioning. Daily drinking and craving for alcohol will be assessed online using Qualtrics software, already in use by our group, and responses will be reviewed with participants in the sessions. Subjects will be referred for treatment if they are interested. They will also be given the 24-hour contact information to reach these psychiatrists at discharge.

The importance of the alcohol sessions is that these provide a clinical measure of craving and the subjective effects of alcohol, which has been a missing component of previous rTMS studies. While self-report scales have been developed to measure craving, these cannot quantify the craving induced by actual alcohol. We will further attenuate the risks by clarifying in the consent form that subjects can decline the dose, and potential participants who are in need or requesting standard of care treatment will be referred to a clinical treatment center. Subjects will be clearly informed that this is a research study investigating rTMS, the efficacy of which is not known, and includes a sham group.

3) Risk of alcohol withdrawal. There is a risk that AUD subjects will experience withdrawal from alcohol. However, as specified in the approach section of the application, subjects will be closely monitored on an inpatient psychiatric unit. The physicians involved in this study (Drs. Wai/Martinez/Nunes) have extensive experience managing AUD subjects and

withdrawal. The risks of alcohol withdrawal include tremors, anxiety, discomfort, and if severe, seizures and death. The management of alcohol withdrawal is discussed below.

4) **MRI scanning.** It may be uncomfortable to lie motionless in the scanner (MRI) and it may cause some subjects to feel anxious. While there have been no reports of any long-term effects caused by magnets of the same or even higher strength, the long-term effects of being placed in a magnet of this strength (3 Tesla) are unknown. The MRI scanner uses a large magnet to take pictures of the brain and is not associated with any known medical risks, except for persons who have a heart pacemaker, or have metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be asked to notify us if this is the case. There is also the risk of burns from medicinal patches during the MRI; therefore, subjects will be asked to remove any patches prior to the scanning session. Also, although there are no known risks associated with pregnancy, we will not scan someone who is pregnant. Therefore, for women of childbearing years, pregnancy testing will be conducted the day of the MRI. Some people have reported sensations during the MRI scan such as “tingling” or “twitching” (or, very rarely a painful sensation), which are caused by changes in the magnetic field that can stimulate nerves in your body.

Occasionally, some people experience nervousness or claustrophobic feelings due to the scanner’s small space. Despite these sensations, in our experience, no one has had sensations from the scanning that did not stop as soon as the scanning stopped.

Adequacy of protection against risks

a. Recruitment and informed consent

Subjects will be recruited through local newspaper, local flyers, and online advertising. The first phase of recruitment is a structured telephone interview when the initial contact is made. Potential participants who report current psychiatric problems, a history of a major axis I disorder, or significant medical/neurological disorders will not be enrolled and will be referred for treatment. Participants passing the initial interview receive a physical exam, medical history evaluation, and psychiatric interview. In addition, laboratory studies (CBC, electrolytes, liver function studies, urinalysis) and ECG will be obtained. Only those judged psychiatrically and physically healthy are accepted to participate.

The nature and the risks of the procedures, as well as the financial remuneration for participating in the study, will be discussed with each subject prior to obtaining informed written consent by a study physician. Subjects will be notified that they may decide to leave the study at any time and will be compensated for the part of the study they have completed. Subjects will receive a complete medical, neurological and psychiatric evaluation and the results will be communicated to the subjects.

b. Protection against risk

All material will be identified by a code number to protect the confidentiality of the subjects. All information obtained from subjects is coded and kept locked in confidential files.

1) *Potential effects of high frequency rTMS:* The risk of high frequency rTMS will be minimized by excluding subjects with a history of seizures, glaucoma, hearing problems, cardiac disease, any neurological disorder, history or current symptoms of a mood or psychotic disorder, or those with a personal or first degree family history of any clinically defined neurological disorder, including organic brain disease, epilepsy, stroke, brain lesions, or multiple sclerosis. Prior to study entry, labs and an EKG will be obtained and the subjects will be seen by a study physician who will obtain a medical and psychiatric history and perform a physical and neurological exam. Although a seizure is not expected, seizure precautions will be used. In the event of a seizure, the procedures outlined above will be followed. **A physician or a nurse trained in seizure management will be present for the first three rTMS sessions and then immediately available and in the building for all rTMS sessions thereafter.**

2) *Risks of alcohol exposure:* The risk of alcohol administration will be minimized by the following: 1) including only participants whose regular use exceeds the amount that can be taken as part of this study. During the screening process, potential participants are asked to quantify their use, without being informed the amounts used in this study. The majority of participants who screen at our facility use alcohol on a regular basis, with binges occurring frequently; 2) throughout the alcohol sessions, the participants are closely monitored. A psychiatrist is immediately available in the adjacent room; 3) as described above, subjects will not be discharged until at least 48 hours have passed since their

alcohol consumption; 4) Participants will be closely followed medically after discharge. They will have access to emergency numbers for psychiatrists and will have an appointment scheduled for within two days of discharge; 5) Potential participants who are unwilling to participate in a research study that includes alcohol and a placebo group will be referred elsewhere for treatment. This also applies to subjects who are determined by the clinical staff to need immediate treatment; 6) alcohol self-administration sessions are needed to model actual drinking. The use of placebo rather than alcohol during the self-administration sessions would not provide the relevant clinical information on whether rTMS treatment would decrease the initiation (i.e., latency) and number of alcoholic drinks consumed; 7) Subjects are not required to perform the second alcohol self-administration session. Subjects who choose not to perform the second session will be allowed to complete the rTMS and participate in the self-administration sessions.

3) *Risks of alcohol withdrawal:* The risks associated with alcohol withdrawal will be minimized by close clinical and vital sign monitoring on an inpatient unit. This includes obtaining the Clinical Institute Withdrawal Assessment Scale for Alcohol-revised (CIWA-Ar) and clinical judgment. Participants requiring lorazepam for withdrawal will be treated with 2-4 mg by mouth every 6 hours as need for 4 doses followed by 1-2 mg by mouth every 6 hours as needed for 8 doses, as per standard management of alcohol withdrawal. Vital signs and the CIWA will be obtained Q 6 hours, and PRN dosing of lorazepam will be administered if needed. In our experience, the majority of individuals without a prior history of medical detoxification do not require lorazepam to manage withdrawal symptoms. Those who do require lorazepam will only continue in the study if they tolerate the three-day lorazepam dosing described above without rescue. An additional three days of medication free inpatient monitoring will be required prior to starting the rTMS protocol. Participants requiring longer dosing of lorazepam will be maintained on the inpatient unit they are fully detoxified and then referred for outpatient treatment.

4) *MRI scanning:* Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the machine if requested. We will screen subjects for heart pacemaker, or any other metal in their body (e.g. shrapnel or surgical prostheses) which may be affected by the magnet. Subjects will be asked to remove any medicinal patches prior to the scanning session. For women of childbearing years, pregnancy testing will be conducted at screening and again on the day of the MRI. If the subject experiences unpleasant sensations or feels uncomfortable, the MR technologist will stop the scan immediately.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data is anonymous. Also, indicate where the data is stored, who is responsible for its safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data is not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Participants divulge information, for example, regarding drug use, which is sensitive and may have adverse social consequences if released. We deal with issues of confidentiality by using coded records, storing signed consent forms in a locked safe, and try to the best of our ability to maintain confidentiality. Data are kept on a password protected computer, and if there is any electronic transmission concerning the study, it will use numeric identifiers rather than participant names. Brainsway, the company providing the H-coil, will not have access to participant records. We also point out to prospective participants that we cannot assure that their drug histories and other personal records might not become known. Those who are hospitalized have hospital charts and we cannot guarantee the confidentiality of these. In addition, we inform volunteers that we must conform with NY State reporting requirements (e.g., child abuse). In addition to a discussion of this topic, the information is clearly stated in our consent forms. Participants in other

studies have understood this and have agreed to participate under these conditions. We will conduct this study under a Certificate of Confidentiality.

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

Given that this study is designed to investigate the efficacy of rTMS in AUD, there are no known benefit to subjects from the rTMS..

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